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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/989,758	11/20/2001	Todd R. Golub	2825.2024-002	9648

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EXAMINER
GUNTER, DAVID R

ART UNIT	PAPER NUMBER
1634	7

DATE MAILED: 12/18/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/989,758	GOLUB ET AL.	
	Examiner	Art Unit	
	David R. Gunter	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,8,15-20 and 37-40* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,8,15-20 and 37-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Applicant's election of group I, claims 1-5, 8-10, 15-20, 23, and 24 in Paper No. 6, dated September 23, 2002 is acknowledged. Because applicant did not distinctly and specifically point out any supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

2. This action is in response to paper number 6 filed September 23, 2002 in which claims number 9, 10, 23, and 24 were cancelled, and claims 37-40 were added. Claims 1-5, 8, 15-20, and 37-40 and are under prosecution.

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1-5, 8, 15-20, and 37-40 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The claims a drawn to a method of classifying a lymphoma sample according to predicted treatment outcome comprising the steps of: (a) isolating a gene expression product from at least one informative gene from one or more cells in said sample; and (b) determining a gene expression profile of at least one informative gene, wherein the gene

expression profile is correlated with a treatment outcome, thereby classifying the sample with respect to treatment outcome.

While the specification and prior art are enabling for classification of a lymphoma sample by determining expression of a bcl-6 gene re-arrangement, the specification and prior art are not enabled for the invention as claimed. There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirements and whether undue experimentation would be required to make and use the claimed invention (see In re Wands, 858 F. 2d 731, 737, 8 USPQ 2d 1400, 1404, 1988). These factors include but are not limited to:

Breadth of the Claims

The claims are drawn to a method of classifying a lymphoma sample based on determining the gene expression profile of at least one informative gene. The specification teaches that "[i]nformative genes include, but are not limited to, those shown in Figures 1, 2A, 2B, 3A, 3B, 4A, and 4B" (page 8, line 29 - page 9, line 1). As broadly as claimed, the phrase "informative gene" encompasses any gene within a cell. The recitation that the method determines the expression level of "at least one" informative gene causes the claims to read on determining the expression level of any combination of any number of genes found in the lymphoma sample, ranging from any single gene to the entire genome. The claims recite that the method of the instant application can be used to classify a sample with respect to treatment outcome (claim 1), including survival after treatment (claim 8), and that the sample can be classified according to lymphoma type (claim 15). These claims recite very broad categories

into which the samples can be classified, and read on any classification system that makes distinctions between types of lymphoma on any basis.

Amount of Direction and Guidance

The specification teaches on pages 13 - 14 "a set of [approximately 100] informative genes ... as shown in Figures 1, 2A, and 2B" that were determined to be correlated to Diffuse Large Cell Lymphoma (DLCL) using a weighted voting method and a "k-Nearest Neighbors" algorithm. Although the specification discloses this list of approximately 100 genes associated with DLCL, it does not disclose the nature of the relationship between the expression of any of these genes and the presence of DLCL. There is no teaching as to which genes, if any, demonstrate an increased level of expression and which genes, if any, demonstrate a decreased level of expression if DLCL is present. In the absence of any teaching demonstrating how the genes are informative, one of skill in the art would not know the specific changes in gene expression that would predict the presence of DLCL.

The claims recite that the method of the instant application can be used to classify a sample with respect to treatment outcome (claim 1), including survival after treatment (claim 8), and that the sample can be classified according to lymphoma type (claim 15). The specification offers no guidance to one of skill in the art that would allow the skilled practitioner to determine the treatment outcome, patient survival, or lymphoma type of a sample based on changes in gene expression. The specification asserts that "[u]tilizing these genes, patient survival can be predicted with high accuracy ($p<0.004$)" (page 14, lines 20-21), but does not give any guidance regarding how the changes in the expression level of specific "informative genes" predicts

patient survival, nor does the specification teach how the accuracy of the predictions was determined.

State of the Prior Art

The state of the prior art is taught by Golub, et al., Science 286:531-537, 1999 (hereinafter "Golub"). Golub teaches a method identical to that of the instant application, which is used to measure the expression level of informative genes in Acute Lymphoblastic Leukemia (ALL) and Acute Myeloid Leukemia (AML). Golub uses the method to measure gene expression of 50 informative genes, and to classify 38 samples as either ALL or AML (page 532, right column, paragraphs 3-5). Golub asserts that the "methodology of class prediction can be applied to any measurable distinction among tumors. Importantly, such distinctions could concern a future clinical outcome" (page 533, left column, last paragraph). Despite this assertion, no guidance is provided by Golub to the skilled practitioner that would allow them to correlate the specific changes in specific genes to the classification or outcome of lymphoma.

Existence of Working Examples

The specification offers one working example, which purports to identify approximately 100 "informative genes" associated with DLCL. The specification asserts that "[u]tilizing these genes, patient survival can be predicted with high accuracy ($p<0.004$)" (page 14, lines 20-21), but does not give any guidance regarding how the changes in the expression level of specific "informative genes" predicts patient survival, nor does the specification teach how the accuracy of the predictions was determined.

Level of Predictability in the Art

It is not within the scope of the present office action to perform a complete analysis of the level of predictability for the correlation between each of the genes of Figures 1, 2A, and 2B and the classification of lymphoma samples. As a representative example, the analysis will focus on HOXA9. HOXA9 is taught by Golub to be the "single most highly correlated gene out of the 6817 genes" tested for the correlation to leukemia (page 533, center column, first paragraph). Drabkin, et al., Leukemia 16(2):186-195, 2002 (hereinafter "Drabkin") used quantitative RT-PCR to examine the expression of HOX family members in 34 cases of AML. Drabkin demonstrated "a significant correlation between event-free survival and HOXA7, with a trend toward significance for HOXA9" (abstract; emphasis added). Although Drabkin teaches a trend toward correlation between HOXA9 and survival in patients with AML, this correlation does not rise to the level of statistical significance. Drabkin further states that "although HOX over-expression and clinical resistance to chemotherapy often coincide, they are not inextricably linked" (abstract; emphasis added). Calvo, et al., Oncogene 21(27):4247-4256, 2002 (hereinafter "Calvo") teach that elevated expression of HOXA9 "is not sufficient to cause rapid AML" (Calvo, abstract). Based on the teachings of Drabkin and Calvo, one of skill in the art would conclude that there is significant unpredictability when attempting to correlate expression of informative genes identified by the current method to the classification of tissue samples.

Quantity of Experimentation Required

In order to use the method of the instant application, one of skill in the art would be forced to perform excessive trial and error experimentation in order to determine which genes would be "informative" for a given type of lymphoma, and how changes in the expression of those genes classify or predict the outcome of the lymphoma. One of skill in the art would be forced to collect samples from a statistically significant number of individuals with lymphoma, extract mRNA from each sample, and then hybridize the mRNA to microarrays to determine the level of expression of every gene in the sample. This determination would be performed three times for each sample to insure that the observed changes are statistically significant and not the result mis-handling the sample. One of skill in the art would also be required to obtain tissue samples from normal individuals to function as controls, and to determine the pattern of gene expression in the control samples in triplicate.

Following determination of the changes in gene expression for each sample, one of skill in the art would then have to objectively classify each sample, and wait (possibly for several years) to determine the clinical outcome for each patient from which a sample was isolated. After objective classification of the samples and determination of clinical outcome, one of skill in the art could then begin the process of determining which changes in gene expression are correlated with either classification or outcome in a statistically significant manner. Only after these steps are complete, and assuming that meaningful correlations are discovered, could one of skill in the art use the method of the instant application to classify a lymphoma sample or predict its clinical outcome.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1-5, 8, 15-20, and 37-40 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 1-5, 8, and 37-38 are indefinite because of the recitation in claim 1 that "the gene expression profile is correlated with a treatment outcome." The term "correlated" is a non-specific relational term, therefore the relationship between the gene expression profile and treatment outcome is undefined. It is suggested that the claim be amended to define this relationship.

b. Claims 15-20 and 39-40 are indefinite because of the recitation in claim 15 that "the gene expression profile is correlated with a lymphoma type." The term "correlated" is a non-specific relational term, therefore the relationship between the gene expression profile and lymphoma type is undefined. It is suggested that the claim be amended to define this relationship.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 1-4, and 15-19 are rejected under 35 U.S.C. 102(b) as being anticipated by Dalla-Favera and Raju, USPN 5,882,858, filed May 28, 1996, issued March 16, 1999 (hereinafter "Dalla-Favera").

a. Claim 1 of the instant application recites a method of classifying a lymphoma sample according to predicted treatment outcome comprising the steps of: (a) isolating a gene expression product from at least one informative gene from one or more cells in said sample; and (b) determining a gene expression profile of at least one informative gene, wherein the gene expression profile is correlated with a treatment outcome, thereby classifying the sample with respect to treatment outcome.

Dalla-Favera teaches a method of classifying a lymphoma sample according to predicted treatment outcome comprising the steps of (a) isolating a gene expression product from at least one informative gene from one or more cells in said sample; and (b) determining a gene expression profile of at least one informative gene (column 10, lines 29-42). Dalla-Favera teaches that the gene expression profile determined by this method correlates to treatment outcome, thereby classifying the sample with respect to treatment outcome (figure 18; also column 36, lines 17-21 and lines 40-45).

b. Regarding claim 2, Dalla-Favera teaches the embodiment in which the lymphoma is Diffuse Large Cell Lymphoma (figures 12 and 13).

c. Regarding claim 3, Dalla-Favera teaches the embodiment in which the gene expression product is mRNA (column 10, lines 29-42).

d. Regarding claim 4, Dalla-Favera teaches the embodiment in which the gene expression profile is determined using hybridization probes specific to at least one informative gene (column 10, lines 29-42).

e. Claim 15 of the instant application recites a method of classifying a sample according to lymphoma type comprising the steps of: (a) isolating a gene expression product from at least one informative gene from one or more cells in said sample; and (b) determining a gene expression profile of at least one informative gene, wherein the gene expression profile is correlated with a lymphoma type, thereby classifying the sample with respect to lymphoma type.

Dalla-Favera teaches a method of classifying a sample according to lymphoma type comprising the steps of: (a) isolating a gene expression product from at least one informative gene from one or more cells in said sample; and (b) determining a gene expression profile of at least one informative gene (column 10, lines 29-42). Dalla-Favera teaches that the gene expression profile determined by this method correlates to lymphoma type, thereby classifying the sample with respect to lymphoma type (Figures 4A-4C, and Figure 6).

f. Regarding claim 16, Dalla-Favera teaches the embodiment in which the lymphoma is Diffuse Large Cell Lymphoma (figures 12 and 13).

g. Regarding claim 17, Dalla-Favera teaches the embodiment in which the lymphoma is follicular lymphoma (column 1, lines 33-34)

h. Regarding claim 18, Dalla-Favera teaches the embodiment in which the gene expression product is mRNA (column 10, lines 29-42).

i. Regarding claim 19, Dalla-Favera teaches the embodiment in which the gene expression profile is determined using hybridization probes specific to at least one informative gene (column 10, lines 29-42).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 5, 20, and 37-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dalla-Favera in view of Perou, et al., Proc. Natl. Acad. Sci. USA 96:9212-9217, 1999 (hereinafter "Perou").

a. Claim 1 of the instant application recites a method of classifying a lymphoma sample according to predicted treatment outcome comprising the steps of: (a) isolating a

gene expression product from at least one informative gene from one or more cells in said sample; and (b) determining a gene expression profile of at least one informative gene, wherein the gene expression profile is correlated with a treatment outcome, thereby classifying the sample with respect to treatment outcome. Claim 3 recites the additional limitation to claim 1 that the gene expression product is mRNA. Claim 5 recites the additional limitation to claim 3 that the gene expression profile is determined using oligonucleotide microarrays.

Dalla-Favera teaches a method of classifying a lymphoma sample according to predicted treatment outcome comprising the steps of (a) isolating a gene expression product from at least one informative gene from one or more cells in said sample; and (b) determining a gene expression profile of at least one informative gene (column 10, lines 29-42). Dalla-Favera teaches that the gene expression profile determined by this method correlates to treatment outcome, thereby classifying the sample with respect to treatment outcome (figure 18; also column 36, lines 17-21 and lines 40-45). Dalla-Favera teaches the embodiment in which the gene expression product is mRNA (column 10, lines 29-42).

Dalla-Favera does not specifically teach that the gene expression profile is determined using oligonucleotide arrays, but rather teaches that the gene expression profile is determined using northern blots and Southern blots. However, the use of microarrays to determine differences in gene expression between normal cells and tumor cells was well known to those of ordinary skill in the art at the time the application was filed. Perou, for example, teaches the use of DNA microarrays to demonstrate

differences in the pattern of gene expression between normal human mammary epithelial cells and breast cancer (figure 1). It would have been obvious to one of ordinary skill in the art at the time the application was filed to modify the method of Dalla-Favera to include a microarray as taught by Perou because the demonstrated ability of the microarray to detect changes in a broad variety of genes in a single experiment (see, for example figure 1). One of ordinary skill in the art would have been motivated to use a microarray because of the increased convenience compared to performing a large number of northern or Southern blots.

b. Claim 15 of the instant application recites a method of classifying a sample according to lymphoma type comprising the steps of: (a) isolating a gene expression product from at least one informative gene from one or more cells in said sample; and (b) determining a gene expression profile of at least one informative gene, wherein the gene expression profile is correlated with a lymphoma type, thereby classifying the sample with respect to lymphoma type. Claim 18 recites the additional limitation to claim 15 that the gene expression product is mRNA. Claim 20 recites the additional limitation to claim 18 that the gene expression profile is determined using oligonucleotide microarrays.

Dalla-Favera teaches a method of classifying a lymphoma sample according to predicted treatment outcome comprising the steps of (a) isolating a gene expression product from at least one informative gene from one or more cells in said sample; and (b) determining a gene expression profile of at least one informative gene (column 10, lines 29-42). Dalla-Favera teaches that the gene expression profile determined by this method

correlates to treatment outcome, thereby classifying the sample with respect to treatment outcome (figure 18; also column 36, lines 17-21 and lines 40-45). Dalla-Favera teaches the embodiment in which the gene expression product is mRNA (column 10, lines 29-42).

Dalla-Favera does not specifically teach that the gene expression profile is determined using oligonucleotide arrays, but rather teaches that the gene expression profile is determined using northern blots and Southern blots. However, the use of microarrays to determine differences in gene expression between normal cells and tumor cells was well known to those of ordinary skill in the art at the time the application was filed. Perou, for example, teaches the use of DNA microarrays to demonstrate differences in the pattern of gene expression between normal human mammary epithelial cells and breast cancer (figure 1). It would have been obvious to one of ordinary skill in the art at the time the application was filed to modify the method of Dalla-Favera to include a microarray as taught by Perou because the demonstrated ability of the microarray to detect changes in a broad variety of genes in a single experiment (see, for example figure 1). One of ordinary skill in the art would have been motivated to use a microarray because of the increased convenience compared to performing a large number of northern or Southern blots.

c. Regarding claims 37 and 38, the claims recite the additional limitations to claim 1 that the gene expression product is isolated from at least five (claim 37) or ten (claim 38) informative genes. Perou teaches the embodiment in which the expression product is isolated from 22 genes (figure 3A).

d. Regarding claims 39 and 40, the claims recite the additional limitations to claim 15 that the gene expression product is isolated from at least five (claim 39) or ten (claim 40) informative genes. Perou teaches the embodiment in which the expression product is isolated from 22 genes (figure 3A).

Conclusion

8. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David R. Gunter whose telephone number is (703) 308-1701. The examiner can normally be reached on 9:00 - 5:00 M - F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones can be reached on (703) 308-1152. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 746-9212 for regular communications and (703) 308-8724 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0198.

David R. Gunter, DVM, PhD
December 16, 2002